REMARKS

Formal Matters

Applicants thank the Examiner for the telephonic interview of June 10, 2003. Applicants have amended claims 1, 4, 6, and 7, and added new claims 9-33. Applicants have also canceled claims 2, 3, and 5. Support for these amendments may be found in the specification at, for example, the following locations:

Claim	Support
1, 33	page 2, lines 3-6; original claim 5; page 6, line 21 to page 7, line 8
4, 14, 25	page 17, lines 1-2
16, 27	original claim 6
17, 28	original claim 7
18, 29	original claim 8
9, 19, 30	page 2, lines 3-5
10, 20, 31	page 18, lines 12-16; page 22, lines 11-19
11, 21, 32	page 18, line 13; page 22, line 17
12, 15, 26	page 17, line 4
13	original claim 1; page 2, lines 3-6; page 79 lines 1-2
22, 23	page 3, lines 13-23; sentence spanning pages 6-7; page 27, lines 16-21
24	page 1, lines 20-22

Claims 1, 4, and 6-33 are now pending in this application.

Indefiniteness Rejection

The rejection of claim 4 for indefiniteness was maintained by the Examiner, despite Applicants' previous argument that the terms "fragment" and "modified" are

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defined in the specification as they relate to the use of antibodies. Further, the Examiner stated "although the claims are interpreted in light of the specification, limitations from the specification are not read into the claims."

In addition to interpreting the claim in light of the specification, claim language must also be analyzed by the teachings of the prior art and as one of ordinary skill in the art would understand the claim. The term antibody "fragment" is understood with a reasonable degree of clarity by one of ordinary skill in the art to mean a portion of an antibody that retains binding specificity for a particular antigen. In addition, teachings of the prior art define different parts of an antibody, such as Fab and scFv that conform to this definition. Indeed, the specification recites at page 17, lines 1-2 that an antibody within the scope of the invention encompasses any fragment or modified product of a fragment that can "bind to PTHrP and inhibit the activity of the PTHrP." Finally, Applicants add dependent claim 12 to more clearly describe these particular fragments.

Nevertheless, to address the alleged indefiniteness of the term "modified," Applicants have removed this limitation from claim 4 and added new claims 10 and 11 to better describe the invention. New claims 10 and 11 are supported in the specification on page 22, lines 13-19.

The Examiner rejected claim 4 as allegedly being indefinite by using the limitation "wherein the substance is at least one of a fragment of an anti-PTHrP antibody or a modified form of the fragment." Office Action at page 8. The Examiner suggests that if Applicants replace the "or" with "and," the claim would be proper. This rejection is moot as Applicants have amended claim 4 for other reasons.

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The Examiner rejected claims 1-8 under 35 U.S.C. §112, second paragraph because "the former claims were drawn to a therapeutic agent comprising a substance that is capable of inhibiting the binding of PTHrP to a receptor thereof, while the present claims are drawn to a method comprising administering to a patient a substance capable of inhibiting the binding of PTHrP to a receptor thereof." As MPEP § 2172 states, "(t)he second paragraph of 35 U.S.C. 112 does not prohibit applicants from changing what they regard as their invention during the pendency of the application." Thus, Applicants request that the Examiner withdraw this rejection.

During the telephonic interview of June 10, 2003, the Examiner indicated that he would prefer use of the phrase "chosen from at least one of" in claim 12 and suggested that this amendment in addition to those discussed above would overcome the indefiniteness rejections. Therefore, Applicants respectfully request that these rejections be withdrawn.

New Written Description Rejection

The Examiner made a new written description rejection of claims 1-8 under 35 U.S.C. § 112, first paragraph. The Examiner stated that "the specification does not describe the production of a substance that is capable of preventing a symptom of a hypercalcemic crisis; furthermore, the specification does not describe the use of such a substance to prevent a symptom of a hypercalcemic crisis." Applicants have amended claim 1 to delete the objected-to word "preventing" merely to facilitate prosecution, although Applicants believe this concept is supported in the specification. As the

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Examiner also indicated in the telephonic interview of June 10, 2003 that this amendment would overcome the rejection, Applicants respectfully request that the Examiner withdraw this rejection.

New Enablement Rejection

The Examiner made a new enablement rejection of claims 1-8 under 35 U.S.C. § 112, first paragraph. The Examiner stated that:

> the teachings of the specification cannot be extrapolated to the enablement of the claimed invention because the amount of guidance, direction, and exemplification set forth therein is insufficient to enable the skilled artisan to have a reasonable expectation of successfully using the claimed invention to prevent or treat a symptom of hypercalcemia or an acute crisis thereof without having the need to perform additional, undue experimentation.

Office Action at page 5.

Applicants point the Examiner to Reference Examples 1-5, which clearly outline the process of making humanized PTHrP antibodies and confirmation of their functional activity. The specification enables a skilled artisan to use the claimed invention, as use of a humanized PTHrP antibody to treat hypercalcemic model rats is described in Example 2 and Figures 1-6. Animal models are acceptable evidence of enablement. Further, means of administration of the antibody and dosages are described in the specification at page 21, line 20 to page 23, line 5. Thus, one of ordinary skill in the art based on these teaching would be able to both make and use the humanized antibodies of the invention. In light of the amendment to claim 1, and these arguments, Applicants request that the Examiner withdraw this rejection.

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The Examiner rejected claims 1-8 under 35 U.S.C. § 112, first paragraph, for containing the following phrases:

1. "method for preventing or treating at least one symptom of hypercalcemic crisis;"
2. "administering to a patient at least one substance;" and
3. "wherein said substance is at least one of a fragment . . . or a modified form of the fragment"

because "there does not appear to be proper and sufficient antecedent basis in the specification for recitation of this claim language." Office Action at page 7. The Examiner also stated that "recitation of such claim language appears to introduce new matter." Specifically, Applicants believe that the Examiner is objecting to the term "at least one" in all of the quoted phrases.

There is no requirement that the words in the claim must match those used in the specification disclosure. As MPEP §2163(I)(B) "While there is no *in haec verba* requirement, newly added claim limitations must be supported in the specification through express, implicit, or inherent disclosure." Applicants believe that this claim language is supported in the specification, but in order to advance prosecution, have removed the term "at least one" from the claims. As the Examiner also indicated in the telephonic interview of June 10, 2003 that this amendment would overcome the rejection, Applicants request that the Examiner withdraw this rejection.

New Anticipation Rejections

The Examiner rejected claims 1, 2, and 8 as being anticipated by both Rosen et al. (Calcified Tissue International 61:455-459, 1997) and WO 92/00753. The Examiner

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further asserted that both Rosen et al. and WO 92/00753 teach a method that comprises administering to a patient a polypeptide agonist or antagonist that is capable of inhibiting the binding of PTHrP to a receptor thereof. Claims 1-5 and 7-8 were also rejected by the Examiner as being anticipated by Yoneda et al. (U.S. Patent 5,626,845). Yoneda et al. teach a monoclonal antibody directed against PTHrP and mention that this antibody may be humanized.

Applicants traverse this rejection. None of the references teach a method for treating **hypercalcemic crisis**. The references discuss treatment of simple hypercalcemia. There are at least three main differences between hypercalcemia and hypercalcemic crisis. First, hypercalcemic crisis is characterized by more serious symptomology, such as impaired consciousness. As described in the specification, "[w]hen hypercalcemia becomes more worsened, impaired consciousness such as general malise, [l]ethargy, and confusion occurs, which may eventually result in coma and cardiac arrest." Specification, page 2, lines 3-5. This aspect is now clearly recited in the claims by Applicants addition of the phrase "hypercalcemic crisis associated with impaired consiousness." *See, e.g.*, claims 1, 13, and 22.

Second, the levels of blood calcium associated with hypercalcemic crisis are defined and are greater than those in simple hypercalcemia. Exhibit 2, provided in the Office Action Response of September 20, 2002, cited in the specification at page 2, lines 5-6 and incorporated in its entirety on page 79, lines 1-2 describes that when the blood calcium level becomes 3.7-4.5 mmol/l (15-18 mg/dl) or greater, there is concern about coma or cardiac arrest occurring. Harrison's Text for Internal Medicine, page

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